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Recombinant Human Interferon α-2b (rh IFNα-2b) Therapy for Steroid Resistant Idiopathic Thrombocytopenic Purpura (ITP)

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The efficacy of recombinant human interferon α-2b (rh IFNα-2b) in the treatment of steroid resistant idiopathic thrombocytopenic purpura (ITP) was studied in 50 cases.

Forty-one patients treated with rh IFNα-2b three times a week, six of 18 (33.3%) in the low dose group (150×10^4IU: 3 MIU) and four of 20 (20.0%) in the high dose group (300×10^4IU: 3 MIU) responded with platelet counts increasing to above 50×10^9/L. Because of the exacerbation of thrombocytopenia and nasal bleeding, treatment was discontinued within 2 weeks in three patients out of 41 cases. On the other hand, six of nine patients (66.7%) treated with 3 MIU of IFNα-2b once a week for 8 weeks showed satisfactory response.

Treatment with either administration schedule did not result in sustaining platelet counts above 50×10^9/L for a long time after treatment. The results indicate that once a week administration schedule of rh IFNα-2b is more efficacious for platelet counts increasing for short period in patients who failed to respond to steroid and other medications than other schedules. The maintenance of this treatment schedule will allow sustained increased platelet levels, resulting in relief of bleeding tendency, while also being cost effective in comparison with other IFN treatment schedules and achieving better patient compliance without flu-like symptoms.

Key words: steroid resistant ITP, interferon α-2b treatment

INTRODUCTION

Corticosteroids are recommended as initial treatment in idiopathic thrombocytopenic purpura (ITP) patients. If corticosteroid therapy does not result in a sustained response, splenectomy is recommended as the second line therapy. However, about 20–30% of ITP patients do not respond well to these conventional treatments and minor bleeding tendency frequently develops. Although several methods of treatment have been attempted to refractory ITP patients, most of them were found not to be entirely satisfactory in refractory ITP [1]. The usefulness of recombinant human interferon α-2b (rh IFNα-2b) in steroid resistant cases was reported by Proctor et al. [2]. Since then, several reports on interferon therapy in refractory ITP have been published [3–6]. However, the results reported were not as favorable as those of Proctor et al. [2].

A multicenter study program was designed to evaluate the efficiency of IFN in steroid resistant ITP. The first part evaluates the dosage of rh IFNα-2b and the second

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part studies different modes and duration of administration to determine the most tolerated and useful treatment schedule.

MATERIALS AND METHODS

Patients

Fifty patients between 5 and 74 years of age were entered into a multicenter study. Informed consent was obtained from these patients or their guardians and ethical problems were cleared by each university or hospital. The diagnosis of chronic ITP was made as follows: 1) continuous bleeding tendency, 2) thrombocytopenia of over 6 months duration, 3) no other peripheral blood cell picture abnormalities, and 4) bone marrow picture showed normal or hyperplastic megakaryocyte poiesis without any abnormal configuration and normal erythroid and granulocyte poiesis.

Patients with other primary or secondary thrombocytopenia were excluded from this study on the basis of bone marrow picture and laboratory data. Patients were defined as not responding to conventional treatment as evidenced by failure to maintain platelet counts over 50×10^9/L. Fifteen of 50 patients did not respond to steroid and splenectomy, and the remaining 35 patients were refractory to steroid and other medication including danazol, immunosuppressive drugs, high dose γ-globulin and ascorbic acid.

Drug

The rh IFNα-2b used in this study was supplied by Schering-Plough Corporation (Osaka, Japan).

Treatment Schedule

The study followed two treatment protocols. The first examined whether efficacy was dosage-dependent. Rh IFNα-2b was administered subcutaneously on alternate days three times a week for 4 weeks. Twenty patients received the low dose (150×10^4IU/total dose in adults, 3×10^4IU/kg but total dose below 150×10^4IU in children) and 21 patients received the high dose (300×10^4IU/total dose in adults, 6×10^4IU/kg but total dose below 300×10^4IU in children). No significant difference was noted between the two dosage groups in patient background factors (Table I). Each protocol was selected by random sampling.

The second treatment protocol was designed to examine the effective dose schedule. Nine patients were given rh IFNα-2b (300×10^4IU/total dose) subcutaneously once a week for 8 weeks. The background of this group was significantly different in sex and pretreatment platelet counts from that of the first treatment protocol (Table I). There were few female, splenectomized patients and no low platelet counts case below 9×10^9/L.

Those patients who were normally on steroid maintenance were continued at the same dose throughout the study, but no additional therapy was given.

Patient Monitoring

In addition to complete blood cell counts, PAIgG (platelet-associated immunoglobulin G) was examined by ELISA method and serum chemistry and urine tests were performed before and after treatment. The plasma and serum from some patients were collected before and after treatment for examination of anti-IFN antibody and IL-6 levels. Surface marker of peripheral lymphocyte was analyzed by flow cytometer.

Statistical Analysis

Statistical analysis was performed by the paired t-test, $\times 2$ analysis or U analysis.

Scale of Response

Complete response (CR): platelet count $\geq 100 \times 10^9$/L without concurrent treatment.
Good response (GR): platelet count $\geq 100 \times 10^9$/L with concurrent treatment.
Partial response (PR): 50×10^9/L $\leq$ platelet count $< 100 \times 10^9$/L.
Minimal response (MR): platelet count $< 50 \times 10^9$/L with increase in platelet count $\geq 20 \times 10^9$/L.
No response (NR): platelet count $< 50 \times 10^9$/L with increase in platelet count $< 20 \times 10^9$/L.
Worsening (W): platelet count $< 50 \times 10^9$/L with diminished platelet count $> 20 \times 10^9$/L.

RESULTS

Efficacy of rh IFNα-2b Administration Three Times a Week in Steroid Resistant ITP

Forty-one patients were entered into this treatment schedule: 20 in the low dose group and 21 in the high dose group. Treatment was discontinued in two patients after two or seven times administration in the low dose and one patient after one administration in the high dose group because of thrombocytopenia and elevation of transaminase in the former and exanthema in the latter. These three patients were excluded from efficacy evaluation but included in safety evaluation. Thus thirty-eight patients were evaluable for response, and safety of this treatment was examined in a total of 41 treatment episodes.

Effect on platelet counts and bleeding symptoms. Platelet counts began to rise after treatment during the first week in both groups and reached the maximum level during the third week in the low dose and the second week in the high dose group (Fig. 1). At the end of this treatment schedule, six of 18 patients (33.3%) in the low dose and four of 20 patients (20.0%) in the high dose group showed good response or partial response (Table

TABLE I. Pretreatment Characteristics of Steroid Resistant ITP Patients

	Low dose [4]	High dose [4]	Once a week [5]	
No of patients	20	21	9	
Sex		p<0.05 [1]		
Male/Female	4/16	7/14	6/3	
		p<0.05 [1]		
Age(yr)				
5~19	2	3	1	
20~39	5	2	3	NS [6]
40~59	10	9	2	
60~	3	7	3	
Performance status				
0	14	12	8	
1	6	9	1	NS [6]
2	0	0	0	
3	0	0	0	
Splenectomy				
Yes	6	8	1	NS [6]
Other previous therapy [2]				
CS [3]	1	2	1	
CS [3] + Immunosuppressive drug	1	2	0	
CS [3] + γ-globulin, Danazol Ascorbic acid etc.	2	4	0	
Chinese herbal remedy	1	0	0	
Blood transfusion	1	0	0	
No	14	13	8	NS [6]
Other previous therapy [2]				
CS [3]	8	5	7	
CS [3] + Immunosuppressive drug	1	2	0	
CS [3] + γ-globulin, Danazol, Ascorbic acid, etc.	4	6	0	
CS [3] + Blood transfusion	0	0	1	
None	1	0	0	
Pretreatment platelet counts($\times 10^9$/L)		p<0.05 [1]		
~ 9	5	7	0	
10 ~ 29	11	9	4	
30 ~ 49	4	5	5	
50 ~	0	0	0	
		p<0.05 [1]		

1): U analysis 2): Within 6 months before rh IFNα-2b
3): Corticosteroid
4): Administration of rh IFNα-2b 3 times a week
Low dose: 150×10^4IU/total dose in aduts
3×10^4IU/Kg but total dose below
150×10^4IU in children
High dose: 300×10^4IU/total dose in aduts
6×10^4IU/Kg but total dose below
300×10^4IU in children
5): Once a week: Once a week administration of rh IFNα-2b
300×10^4IU/total dose
6): NS: Not significant

II). The effectiveness above partial response was not significantly different between the two dosage schedules. Platelet counts also returned to pretreatment levels in most patients after cessation of IFN treatment (Fig. 1). The distribution of platelet counts before IFN treatment was from 4 to 49 $\times$ 10^9/L (mean 19 $\pm$ 2 $\times$ 10^9/L) and after treatment cessation from 2 to 135 $\times$ 10^9/L (mean 35 $\pm$ 6 $\times$ 10^9/L). There were no significant differences in the background between responder and nonresponder cases in both groups.

Five children under 14 years old were able to complete these treatment schedules. Two of them in low dose group and two of three in high dose group showed partial response.

Bleeding tendency including wet bleeding or purpura disappeared in five patients in the low dose and eight

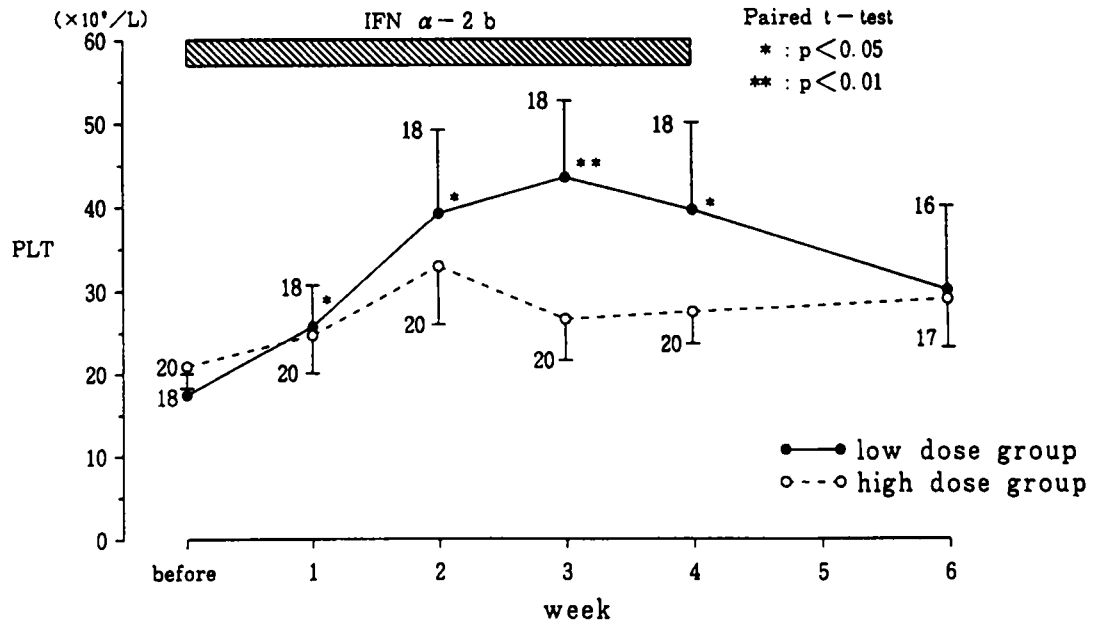

Fig. 1. Time course of platelet counts (mean ± SE) and case number in steroid resistant ITP patients who were treated with rh IFNα-2b three times a week for 4 weeks.

TABLE II. Treatment Results in Steroid Resistant ITP Patients Treated With rh IFNα-2b Three Times a Week for 4 Weeks

Dosage group	No. of patients	Response at end of treatment CR	GR	PR	MR	NR	W
Low dose group	18	0 (0.0)	3 (16.7)	3 (33.3)	1 (38.9)	11 (100.0)	0 (100.0)
High dose group	20	0 (0.0)	0 (0.0)	4 (20.0)	3 (35.0)	12 (95.0)	1 (100.0)
Total	38	0 (0.0)	3 (7.9)	7 (26.3)	4 (36.8)	23 (97.4)	1 (100.0)

( )=accumulation %
Abbreviation: CR, Complete response; GR, Good response; PR, Partial response; MR, Minimal response; NR, No response; W, Worsening; NS, No statistical difference between two groups.

patients in the high dose group, but exacerbation of bleeding tendency was found in two patients in the low dose and one patient in the high dose group.

Effect on laboratory findings. No changes in immunological parameters, such as CD4, CD8, NKH-1 cell percent, CD4/CD8 ratio, immunoglobulin and complement level, were noted before or after treatment in either the responder or non-responder group (Table III). The responder cases showed decrease in PAIgG levels from 373.0 ± 82.2 to 168.7 ± 43.6 ng/10^7plt after treatment while non-responder cases did not (from 466.5 ± 55.1 to 428.8 ± 62.5 ng/10^7plt). Anti-IFN antibody was not detected in the 18 patients examined.

Side effects. In the high dose group, leukocytopenia (<3 × 10^9/L) was noted transiently in three patients (15%: 3/20) and leukocyte count was less than that of the low dose group during treatment, which seemed to indicate mild bone marrow suppression. Thrombocytopenia was found in two patients in the low dose group. The elevation of transaminase was observed in several patients. Exanthema appeared in one case after one administration and this regimen was discontinued. Flu-like symptoms such as fever, general fatigue, headache, and loss of appetite were noted in 21 patients (51.2%). There was no difference in the incidence of side effects between these two treatment groups.

TABLE III. Analysis of Immunological Parameters in Responder and Non-Responders Who Were Treated Three Times a Week for 4 weeks

	Responder		Non responder		Total	
	before	after	before	after	before	after
PAIgG (ng/10^7plt)	373.0±82.2 (n=14)	168.7±43.6	466.5±55.1 (n=20)	428.8±62.5	428.0±46.8 (n=34)	321.7±46.1
IgG (mg/dl)	1221±75 (n=9)	1248±122	1519±149 (n=21)	1401±99	1429±108 (n=30)	1355±78
IgA (mg/dl)	205±18 (n=9)	192±11	275±30 (n=21)	266±24	254±23 (n=30)	244±18
IgM (mg/dl)	131±8 (n=9)	181±45	178±28 (n=21)	179±28	164±20 (n=30)	179±23
C_3 (mg/dl)	80.2±9.0 (n=10)	79.0±6.3	64.1±3.4 (n=17)	59.9±3.4	70.0±4.2 (n=27)	67.0±3.6
C_4 (mg/dl)	22.9±2.5 (n=10)	26.6±1.5	21.8±1.6 (n=18)	23.3±1.6	22.2±1.4 (n=28)	24.5±1.2
CD4/CD8	1.30±0.20 (n=10)	1.53±0.28	1.87±0.31 (n=16)	1.49±0.17	1.65±0.21 (n=26)	1.50±0.15
NKH-1 (%)	9.6±2.1 (n=8)	9.4±2.1	8.6±1.8 (n=14)	10.0±2.4	9.0±1.3 (n=22)	9.8±1.6

Each value represents the mean ± SE. n=number of evaluable patients at analysis.
Responder : patients who achieved good response or partial response during treatment

rh IFNα-2b Administration Once a Week for 8 Weeks

Nine patients were treated according to this schedule. Seven patients completed treatment under this schedule but treatment was discontinued in two patients, one in the third week due to occurrence of side effect (fever elevation) and the other in the fourth week due to lack of effect.

Effect on platelet counts. The platelet count increased within 1 week after starting this treatment (Fig. 2). At the end of this schedule, six of nine patients (66.7%) showed partial response (Table IV). This response rate was higher than that of the three times a week treatment schedule. However, platelet counts returned to pretreatment levels in the second week after completion of this treatment except in three patients. The platelet counts of these three patients returned to pretreatment levels within 3–4 weeks after cessation of IFN. Two patients with bleeding tendency (purpura, gingival bleeding) showed improvement and there was no patient whose bleeding tendency was exacerbated.

Effect on laboratory findings and side effects. There were no specific changes in laboratory data arising from this treatment schedule. There was no leukocytopenia. General fatigue, fever, headache, and loss of appetite were noted in eight patients (88.9%) after each administration. In the case of this intermittent administration schedule, flu-like symptoms occurred after each dose at about the same degree of severity. Tachyphylaxis for flu-like symptoms appeared not to have occurred. No anti-IFN antibody was detected and no significant change in plasma IL-6 levels was observed before or after treatment.

DISCUSSION

The usefulness of IFN therapy in thrombocytopenia associated with HIV or hepatitis B infection was first reported in 1987 [7,8]. One year later, Proctor et al. reported that platelet counts were improved dramatically by IFN in severe unresponsive immune thrombocytopenic purpura [9]. Much attention was drawn to this therapy by the report of elevation of platelet counts in 11 of 13 patients with refractory ITP, with complete recovery in three patients [2]. In this study, 300 × 10^4IU rh IFNα-2b was administered subcutaneously three times a week for 4 weeks. The response rate was high and 10% of patients achieved complete remission. In addition, remission or effective increase in platelet counts was sustained for a long time after termination of treatment.

This treatment was conducted in refractory ITP by several groups, but results similar to that of the report by Proctor et al. were not obtained despite the use of similar

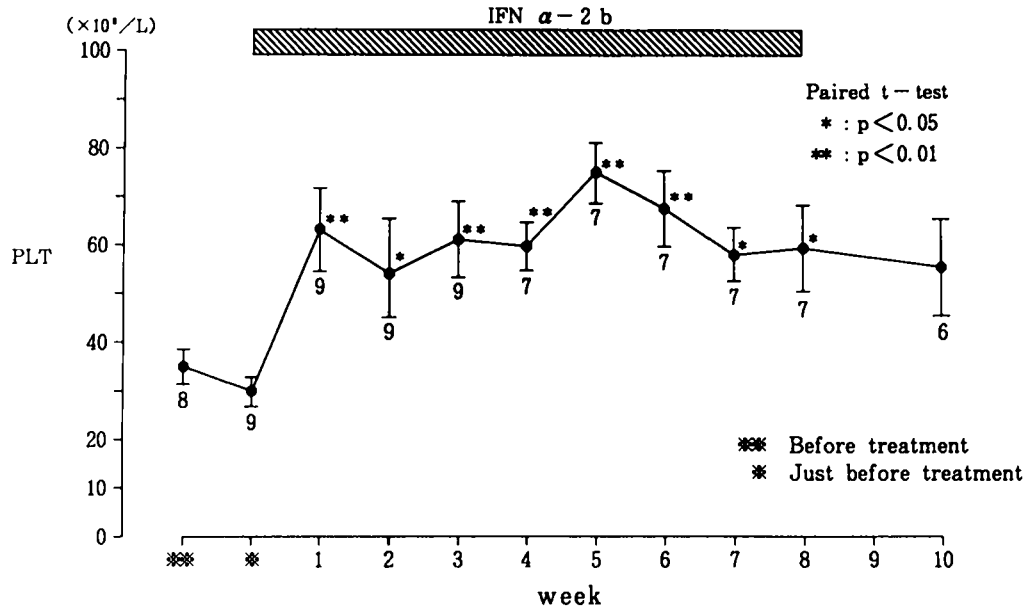

Fig. 2. Time course of platelet counts (mean ± SE) and case number in sterold resistant ITP patients who were treated with rh IFNα-2b once a week for 8 weeks.

TABLE IV. Treatment Results in Nine Patients Treated With rh IFNα-2b Once a Week for 8 Weeks

	Response at end of treatment					
	CR	GR	PR	MR	NR	W
No. of patients	0	0	6	0	3	0
	(0.0)	(0.0)	(66.7)	(66.7)	(100.0)	(100.0)

( )=accumulation %; CR, complete response; GR, Good response; PR, Partial response; MR, Minimal response; NR, No response; W, Worsening

patients and protocol [3–6]. The efficacy rates were low and there was no case of complete response or any long-term response or improvement in bleeding manifestations. In other words, the response was transient and the duration of improvement of platelet counts was less than 2 weeks in most patients.

We conducted a random study to identify the effective dosage of IFN because this drug has dose-dependent suppressive action on bone marrow. A positive platelet count response was experienced more often in the low dose group than in the high dose group. Since in the high dose group the leukocyte count was decreased to the lower limit of normal range, mild marrow suppression in this group might have affected the platelet count. However, in both treatment groups the response was not maintained for any length of time and there was no patient whose platelet count rose with termination of treatment as shown by Proctor et al. [2]. It was difficult to compare the response between adult and children because the number of children were small. The following three points: 1) elevation in platelet count lasted only 1–2 weeks after the end of treatment, 2) the effective dose for platelet response was low, and 3) response appeared early after initial IFN administration, suggested a new treatment schedule which might induce increase in platelets more effectively without bone marrow suppression.

IFN administration (300×10^4IU/total dose) once a week was more effective in one-third of patients and the platelet count was higher than pretreatment levels in the second week after finishing treatment. The side effects observed with this regimen were not different from those previously reported and there were no patients whose bleeding tendency was exacerbated. Most of the patients (8/9) in this group were not splenectomized, and these

pretreatment platelet counts were above 10×10^9/L. These factors might have influenced better response to this treatment schedule than to that of three times a week administration. These findings suggest that 300×10^4IU rh IFNα-2b administered once a week is effective in increasing platelets for short duration, in spite of the statistical limitation that was present because the subject cases were small. Since this effect appeared within 1 or 2 weeks after initiation of IFN administration, it can evaluate early the effect of this treatment. This treatment schedule was cost effective in comparison with other IFN treatment schedules. Overall, as the effectiveness and usefulness of this treatment schedule was equivalent to or better than that of three times a week administration without the high incidence of flulike symptoms, this administration schedule is recommended for one of the treatment strategies of steroid-resistant ITP patients. Maintenance on this new treatment schedule will keep the platelet count over 50×10^9/L and will relieve bleeding episodes, as well as improve the quality of life. More recently, two refractory ITP patients who responded to weekly or monthly administration of IFN were reported [10].

The mechanisms of IFN effect in ITP patients are unknown. The PAIgG levels in patients who responded were decreased after IFN treatment in this study, but the ratio of lymphocyte subset in peripheral blood including NK cell was not different between responders and non-responders, and IL-6 levels were not elevated after this treatment. These data suggest that the cellular immunity or IL-6 level did not affect the increment of platelets directly by IFN treatment. Several articles have reported the elevation of autoantibody titers or development of autoimmune disease after long term IFN treatment in hairy cell leukemia or lymphoma [11]. It is also known that autoimmune thyroiditis or autoimmune hemolytic anemia occurs sometimes during IFN treatment [12–14]. Recently, additional side effects of IFN treatment, interstitial pneumonia and psychiatric symptoms (depression, sleepiness, or irritability), were experienced in chronic hepatitis type C treatment. Similar events during IFN treatment in ITP patients have not been reported to date. However, attention must be paid to these side effects and the aggravation of ITP, and platelet counts and autoantibodies should be monitored carefully during IFN therapy [15–18].

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